Congressional Update: *Report from the Biomedical Imaging Program of the National Cancer Institute*

National Cancer Institute Initiative for Development of Novel Imaging Technologies[1]

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Important advances in medical imaging technologies have been made during the past 25 years in such areas as magnetic resonance imaging, computed tomography, nuclear medicine, and ultrasonography. However, these advances focused largely on structural or anatomic imaging at the organ or tissue level. Furthermore, the research and development costs have traditionally been borne primarily by the medical device manufacturers. There are clearly a need and an opportunity now to stimulate the development and integration of novel imaging technologies that exploit our current knowledge of the genetic and molecular bases of cancer. Those molecular biological discoveries have great implications for cancer prevention, detection, and targeted therapy. Imaging technologies that can provide in vivo the same kind of cellular and molecular information that is currently available only from in vitro techniques would be very useful. This is commonly referred to as in vivo molecular imaging.

The stimulation of such technology development comes at a time when the resources of device and pharmaceutical manufacturers have diminished. Furthermore, their research and development efforts are often focused, for competitive reasons, toward improving patient throughput or making incremental improvements in existing technologies, rather than toward new high-risk technologies. The need for National Cancer Institute (NCI) support of bioengineering and technology development by academia and industry has been articulated in many National Institutes of Health (NIH) forums and NCI-supported workshops over the past 2 years (Imaging Sciences Working Group, July 1997; Lung Imaging Workshop: Technology Transfer, January 1997; Computer-aided Diagnosis and 3D Image Analysis, October 1998; Quantitative in Vivo Functional Imaging in Oncology, January 1999; Focus Group on Magnetic Resonance Spectroscopy in Clinical Oncology, April 1999; and BECON Symposium, June 1999) (1). The needs are to (*a*) promote the development of very novel (high-risk, high-gain) technologies, including continued support for their maturation and full exploitation, (*b*) promote system integration of technologies for targeted applications, and (*c*) improve technology transfer by promoting partnerships between academia and industry.

NIH has supported some technology development over the past several years by means of the R01 mechanism, the Small Business Innovation Research (SBIR) program, and the National Center for Research Resources (NCRR) technology development center grants (ie, P41 grants). However, the traditional R01 mechanism, for example, has not been designed to promote either high-risk or novel technology development or to encourage partnerships with industry to facilitate technology transfer or product development. The NCRR technology development centers have been very successful in fostering some imaging technology development, but the relatively small NCRR budget allows for only a couple of new center awards each year. Therefore, participants in the workshops described above have recommended the creation of a tailored and flexible mechanism to support the development of a diverse array of imaging methods with varying levels of complexity and technologic risk. The workshop

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participants recommended review criteria specifically focused on technology development methods and performance criteria as opposed to evaluation methods based on preclinical models or clinical investigations. The funding mechanism should also provide suitable and flexible support with funding levels and timetables that match the scope of each phase of development (ie, feasibility, system component development, and integration). This modified mechanism should enhance interdisciplinary collaboration among technology developers in academia and industry, in fields such as physics, computer science, bioengineering and molecular biology, and medical imaging. Last year, NIH created the phased innovation award (R21/R33) mechanism that addresses several of these concerns.

In November 1997, NCI issued a program announcement (PA) entitled "Exploratory Development Grants for Diagnostic Cancer Imaging" (PA 98-008) (2). This provides R21 support for both feasibility studies and novel imaging technology development. There has been an excellent response from the imaging community to this initiative. However, there is a need to provide a suitable means of transition from an R21 to another funding mechanism suitable for technology development. In addition, there is a need to support phased innovation, both to promote more innovative high-risk applications for the development of imaging technology and to allow rapid transition from concept to the mature development of technology. The PA entitled "Exploratory Technologies for the Molecular Analysis of Cancer" (PAR 99-100), which was the first implementation of the phased innovation award mechanism (R21/R33), has been very successful, for example, in funding very innovative technologies in the expanding field of molecular biology (3). A recent (August 1999) request for applications also uses the phased innovation award mechanism for imaging applications—namely, "Diagnostic Imaging and Guided Therapy in Prostate Cancer"—and includes a parallel SBIR/Small Business Technology Transfer (STTR) Initiative (4). However, this request for applications is focused specifically on improved imaging methods for the localization, biopsy, and image-guided biopsy or therapy of prostate cancer. The proposed new NCI initiative addresses a much broader spectrum of imaging technology with emphasis on development of novel imaging systems, system integration of emerging novel and traditional imaging technologies for planned targeted applications, and participation by industry that is critical for technology transfer to the larger medical imaging community. In addition, the applications will be reviewed within NCI, because of the innovative nature of this new funding mechansim that is inherently different from the R01 mechanism. The review process may later be transitioned to the Center for Scientific Review if this funding mechanism and PA are successful.

In 1999, the NIH Bioengineering Consortium (BECON) issued PAs to facilitate bioengineering projects. NCI participates in both of these: Bioengineering Research Grants (BRG: PA 99-009) and the Bioengineering Research Partnerships (BRP: PA 99-010) (5,6). Technology development is promoted under both of these PAs with a tailored review mechanism under the Center for Scientific Review. The new NCI initiative will address the specific needs relevant to cancer imaging, and molecular imaging in particular, and will include a parallel and accelerated SBIR/STTR award mechanism, as well.

SCOPE OF THE INITIATIVE (PAR)

This new initiative is directed at the development of image acquisition or enhancement methods, with limited evaluation or feasibility studies using either preclinical models or clinical investigations. The intent is to stimulate (*a*) the development of highly innovative image acquisition and enhancement methods, including high-risk and high-gain technologies that exploit our expanding knowledge of the molecular basis of cancer, and (*b*) the integration of these emerging and more traditional technologies for more effective solutions for cancer.

The motivation for this new initiative is that current technologies for the molecular analysis of cancer are largely restricted to in vitro analysis and need to be extended to in vivo analysis. The development of innovative high-resolution imaging methods at the cellular or molecular scales is needed, with a particular emphasis on identification and characterization of either the early formation of cancer or early molecular changes during intervention or therapy. The use of molecular probes or tracers for imaging molecular events in preclinical or human investigations is often necessary for detection of molecular changes in vivo.

Proposed technologies should address one or more of the following clinical applications:

Imaging to Detect Preneoplasia

The development of innovative, high-resolution imaging methods at the cellular or molecular scales is encouraged, with a particular intent to identify and characterize premalignant abnormalities. Novel solutions for in vivo microscopic imaging methods or microscopic implanted devices with high spatial, contrast, and temporal resolution are encouraged. The imaging methods proposed should emphasize analysis of molecular events on the path to cancer formation.

Large-Scale Cancer Screening Applications

Development and optimization of efficient low-cost imaging systems for rapid and automated large-scale screening with the intent of achieving substantially higher sensitivity and specificity for cancer detection are encouraged. Imaging methods could include substantial innovative improvements to current imaging methods or new imaging sensors, means to reduce imaging time or motion effects, use of contrast agents or imaging probes, and use of technologies that do not involve ionizing radiation. System integration could include a variety of image-processing techniques including temporal analysis of serial studies, close to real-time image processing, novel image display methods, and related informatics and information-reduction methods.

Imaging for Diagnosis, Staging, and Monitoring the Effects of Therapy

This new initiative would encourage the development of novel imaging methods such as functional molecular imaging or spectroscopic methods that would improve the specificity of cancer diagnosis, allow deterministic methods or patient-specific staging, or measure early effects of therapy. System integration would include image fusion or registration from the different modalities employed, development of software methods to estimate the probability of malignancy, quantitative methods for monitoring the effects of therapy, and close to real-time image analysis.

Image-guided Biopsy and Image-guided Therapy

Novel approaches with imaging technologies are needed to improve specificity for identification of lesion extent and microscopic involvement and to minimize the tissue damage accompanying biopsy and therapy. Innovative approaches to image-guided therapy could include novel imaging sensors, system integration of navigational systems, registration methods for several imaging modalities, real-time feedback mechanisms for controlling therapy, or the use of methods that are adaptive or allow patient-specific optimization of treatment.

SUBMISSION OF APPLICATIONS

Under this new PA, applicants can submit either a combined R21/R33 application or the R33 application alone if feasibility can be documented. Applications for R21 support alone will not be accepted in response to this PA but may still be submitted in response to PA 98-008, Exploratory Development Grants for Diagnostic Cancer Imaging. The total project period for an application submitted in response to this new PA should not exceed the following: R33 phase, 3 years; combined R21/R33 application, 4 years. For the combined application, the R21 phase cannot extend beyond 2 years. For the combined R21/R33 applications, the R21 phase may not exceed $100,000 direct costs per year. R21 budgets can exceed this cap to accommodate costs to subcontracts for the project. Although the R33 application has no official budgetary limit, applications requesting in excess of $500,000 direct costs in any single year of the grant period require NCI approval before submission. Small businesses will be directed to a parallel PA of identical scientific scope that uses the SBIR and STTR mechanisms with accelerated review and transition, as well as cost and duration requirements comparable to the phased innovation awards.

The R21/R33 mechanism provides a second phase for the support of innovative exploratory and developmental research initiated under the R21 mechanism. The combined R21/R33 application offers the following advantages over the regular application process and is thus particularly suitable for imaging technology development: (*a*) single submission and evaluation of both the R21 and the R33 as one application, (*b*) expedited transition of feasibility phase to development/system integration phase, (*c*) flexible staging of feasibility and development/system integration phases, and (*d*) flexible budgets that match the different phases of research effort.

To be eligible for the Phased Innovation Award, the R21 phase must include well-defined quantifiable milestones that will be used to judge the success of the proposed research, as well as a credible plan for the development of technology for the R33 phase. The Phased Innovation Award must have a section labeled “Milestones” at the end of the research plan of the R21 application. The award of R33 funds will be based on program priorities, on the availability of funds, and on the successful completion of negotiated scientific milestones as determined by NCI staff in the context of peer-review recommendations.

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